NOVEMBER 2007

BONE DENSITOMETRY IN CHILDREN AND ADOLESCENTS

HEALTH TECHNOLOGY ASSESSMENT UNIT

MEDICAL DEVELOPMENT DIVISION

MINISTRY OF HEALTH MALAYSIA

017/07

Prepared by:

Dr Izzuna Mudla bt Mohamed Ghazali
Principal Assistant Director
Health Technology Assessment Unit
Ministry of Health Malaysia
November 2007

Reviewed by:
Datin Dr Rugayah bt Bakri
Deputy Director
Health Technology Assessment Unit
Ministry of Health Malaysia
November 2007

EXECUTIVE SUMMARY

Bone densitometry is a widely used tool for quantitative assessment of the skeleton. The evaluation of bone density in a child or adolescent has become increasingly common as groups of young patients are recognized to be at risk for osteoporosis.

There is a wide variety of devices available for quantifying bone mineral density in children and adolescents. This include dual-energy X-ray absorptiometry (DXA), quantitative computed tomography (QCT), quantitative ultrasound (QUS), peripheral DXA (pDXA), peripheral QCT (pQCT), peripheral quantitative ultrasound (pQUS) and magnetic resonance imaging (MRI).

This review found that there was fair evidence on the effectiveness of bone densitometry in children and adolescents. It is recommended that a widely acceptable, accurate and feasible bone densitometry measurement such as pDXA be used in epidemiological research.

BONE DENSITOMETRY IN CHILDREN AND ADOLESCENTS

1. INTRODUCTION

The evaluation of bone density in a child or adolescent has become increasingly common as groups of young patients are recognized to be at risk for osteoporosis.[1] Osteoporosis is defined as "skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality. Bone quality refers to architecture, turnover, damage accumulation (e.g microfractures) and mineralization". Because osteoporosis is a silent condition and because there is no clinical tool to assess bone quality, measurement of bone mineral density (BMD) is required to identify patients before fractures occur.[2]

Skeletal mass increases progressively during growth with an accelerated phase at the time of the prepubertal growth spurt.[3] Thus, the amount of bone that is gained during adolescence is the main contributor to peak bone mass, which is a major determinant of osteoporosis and fracture risk in late adulthood.[4] Therefore evaluation of the growing skeleton is the focus of increasing interest in both pediatric and adult medicine.

Bone densitometry is a widely used tool for quantitative assessment of the skeleton. The measurement of bone mineral content (BMC) and bone mineral density (BMD) in children and adolescents has become widely available and pediatric reference databases have been created.[5] There are several methods for measuring BMD and the most widely used is *dual-energy X-ray absorptiometry* (DXA).

This technology review was requested by the Technical Working Group for Research, Family Health Development Division, Ministry of Health Malaysia who will be using bone densitometer for nutrition survey among school children.

2. OBJECTIVES

To determine the safety, effectiveness and cost-effectiveness of densitometers in measuring bone density in children and adolescents.

3. TECHNICAL FEATURES

There is a wide variety of devices available for quantifying bone mineral density in children and adolescents. This include dual-energy X-ray absorptiometry (DXA), quantitative

computed tomography (QCT), quantitative ultrasound (QUS), peripheral DXA (pDXA), peripheral QCT (pQCT), peripheral quantitative ultrasound (pQUS) and magnetic resonance imaging (MRI).

3.1 DUAL ENERGY ABSORPTIOMETRY (DXA)

The fundamental principle of DXA is the measurement of transmission of x-rays with high and low energy photons through the body. Bone mineral is a physically dense material mainly made up of phosphorus and calcium molecules that have relatively high atomic numbers. Soft tissue is a mixture of muscle, fat, skin, and water. It has a lower physical density and a lower effective atomic number because its main chemical constituents are hydrogen, carbon and oxygen. At the same photon energy, soft tissues and bone will have different mass attenuation coefficients. For different x-ray energies, the mass attenuation coefficient will be different. The bone density is determined for each point, or each pixel, of the area being scanned. As the source and detector move linearly across the scanned area, a bone profile is generated on a pixel by pixel basis. The bone density is then made up of many linear passes.[6]

DXA is a projectional technique in which three dimensional objects are analyzed as two-dimensional. DXA provides an estimate of areal BMD in g/cm^2. This BMD is not a measure of volumetric density (in g/cm^3) because it provides no information about the depth of bone. BMD of bones with identical volumetric BMD but varying in size, will differ substantially in areal BMD. Other factors that should be considered when interpreting DXA results in pediatrics include size and projection artifacts, bone detection limitations, and the lack of standardized normative data for children and adolescents.[6]

Nevertheless DXA has numerous strengths as a clinical tool in the field of pediatric densitometry, including its availability, short scan times, minimal radiation exposure and excellent precision. It is the current “gold standard” for diagnosing osteoporosis and for monitoring patients.[2]

Table model DXA machines can measure BMD at the hip or spine but can also be used to measure the total amount of mineral in the whole skeleton or forearm. Peripheral densitometry (pDXA) is a smaller device to measure bone density in the forearm or heel. The distal radius is often used since it contains trabecular and cortical bone.[7]

3.2 QUANTITATIVE COMPUTED TOMOGRAPHY (QCT)

Single energy QCT can accurately account for bone size in three dimensions, permitting determination of a volumetric BMD measurement. QCT of the spine and hip is considered the gold standard for noninvasive evaluation of BMD. The techniques differentiates cortical from

trabecular bone and allows a precise study of the alterations in skeletal size and shape that occur during growth and puberty. Measurements can be obtained using conventional computed tomography or with pQCT scanners. QCT usage is presently hindered by the techniques limited availability, significant radiation dose, high cost and sparse pediatric normative data.[8]

3.3 QUANTITATIVE ULTRASOUND (QUS)

Quantitative ultrasonography (QUS) is an exploratory technique at present but offers the positive features of being portable, inexpensive and radiation free in the evaluation of BMD of peripheral sites. QUS does not measure BMD or BMC directly; it uses broadband ultrasound attenuation and speed of sound (SOS) to estimate BMD.[8]

3.4 MAGNETIC RESONANCE IMAGING (MRI)

Magnetic resonance is a complex technology based on the high –magnetic fields, transmission of radiofrequency (RF waves), and detection of RF signals from excited hydrogen protons. High resolution MR and micro-MR have received considerable attention as research tools and as potential clinical tools for assessment of trabecular bone architecture.[9]

3.5 INTERPRETATION OF BONE DENSITOMETRY

The interpretation of bone density measurements in children is more complicated than in adults since the size, shape and mineral content of bone in children is constantly changing. [10]

The World Health Organization has defined the following categories based on bone density in white women:

Normal bone: T-score better than -1.
Osteopenia: T-score between -1 and -2.5
Osteoporosis: T-score less than -2.5.

However the International Society for Clinical Densitometry (ISCD) has come out with guidelines that this WHO classification should not be applied to children. T-scores should not be used in children; Z scores should be used instead. T-scores should not appear in reports or on DXA printouts in children. The diagnosis of osteoporosis in children should not be made on the basis of densitometric criteria alone. Terminology such as “low bone density for chronological age” may be used if the Z-score is below -2.0.[11] T-scores are used to diagnose osteoporosis, and Z-scores give the physician a sense of age-appropriateness of bone loss.[12]

4. METHODOLOGY

4.1 SEARCH METHODS

Literature were searched through electronic databases, which included Pubmed, OVID, Proquest, Ebscohost, EBM Reviews for controlled trials, Cochrane database on systematic review, Cochrane Clinical Trial Registry, Science Direct, Springer Link, and general databases such as Google and Yahoo. Health technology assessment databases were also searched for relevant articles.

The search strategy used the terms, which are either used singly or in various combinations: densitomet*, "nutritional status" OR "bone density", "adolescent OR child*, effectiveness OR efficacy, safety OR safe OR "adverse effect*" OR "harm* effect*" OR toxicity, "cost effectiveness" OR "cost analysis" OR econom*.

4.2 SELECTION OF STUDIES INCLUDED/EXCLUDED

All primary papers, systematic reviews or meta analysis pertaining to safety, effectiveness and cost effectiveness of densitometer in children and adolescents were included in this study.

A critical appraisal of all relevant literature was performed and the evidence level graded according to the Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001) (Appendix 1).

5. RESULTS AND DISCUSSION

There were 11 primary papers retrieved regarding bone densitometry in children in adolescents.

5.1 SAFETY

The safety issue related to bone densitometry in children and adolescents is the exposure of x-ray dose. There was no primary papers retrieved comparing the safety aspects of bone densitometers. However compared to QCT and pQCT, DXA has lower x-ray dose. QUS techniques however, are radiation free.[5]

5.2 EFFICACY/EFFECTIVENESS

There were various devices that can be used to measure bone mineral density in children and adolescents. Currently DXA is considered as the gold standard for bone mineral density. However, DXA only provided estimate of areal BMD in g/cm^2 and not a measure of volumetric density (in g/cm^3) because it did not provide information about the depth of bone as compared to computed tomography measurements. Wren et al in their study found excellent agreement between DXA-BMC and CT-BMC ($r^2 = 0.94$; $p<0.0001$) which indicates that DXA was as good as CT in bone mineral content (BMC) measurement. They also found low agreement between DXA aBMD and CT vBD, and suggested that BMC was more accurate and reliable than aBMD for assessing bone acquisition.[13] Level 2b In a case control study comparing HIV infected children and adolescents with healthy subjects, Pitulcheewanont et al found that with DXA, vertebral bone area, BMC, BMD and Z-scores were significantly lower in the cases compared to control, however with CT, vertebral BD and Z-scores, the results were similar to controls. However, in this study, comparison with CT-BMC was not done.[14] Level 4

Hernandez Prado et al in their study compared pDXA (PIXI) with central DXA (HOLOGIC) in preadolescent and adolescent women found that BMD in central and peripheral sites were positively associated and has moderate to high correlations even after adjustments. They proposed that pDXA be used as a tool for population based epidemiologic studies and clinic evaluation of high risk women in these age groups.[15] Level 2b

As for ultrasound bone densitometry (QUS), several studies showed that QUS has low correlation with DXA BMD.[16] Level 4, [17] Level 2b, [18] Level 4 Direct x-ray radiogrammetry (DXR) BMD showed moderate to strong correlation with DXA-BMD. [19] Level 2b, [18] Level 4

5.3 COST-EFFECTIVENESS

There was no evidence retrieved on cost-effectiveness of bone densitometry in children and adolescents.

6. CONCLUSION

There are various devices that can be used to measure bone density in children and adolescents. Currently DXA and pDXA is still the most widely used and considered as gold standard although some caution should be taken in interpreting the results.

7. RECOMMENDATION

Based on the findings of this review, it is recommended that a widely acceptable and accurate and feasible bone densitometry measurement such as pDXA be used in this survey.

8. REFERENCES

1 . Gordon CM. Evaluation of bone density in children. Current opinion in Endocrinology and Diabetes. 2005;12:444-451.

2 . Watts NB. Fundamentals and pitfalls of bone densitometry using dual energy absorptiometry (DXA). Osteoporosis International. 2004;15:847-854.

3. Walker-Bone K, Reid DM, cooper C. Is screening for osteoporosis worthwhile. British Medical Bulletin. 1998;54(4):915-927.

4. Pitukcheewanont P, Chen P. Bone density measurements in children and adolescents: Quantitative computed tomography versus dual-energy x-ray absorptiometry. The Endocrinologist. 2005;15(4):232-239.

5 . Bianchi ML. Osteoporosis in children and adolescents. Bone. 2007;41:486-495.

6. Crabtree NJ, Leonard MB. Dual-energy x-ray absorptiometry. In: Sawyer AJ, Bachrach LK, Fung EB (Ed). Current Clinical Practice; Bone densitometry in growing patients: Guidelines for Clinical Practice. Humana Press Inc., Totowa,NJ. c2006.

7. Cummings SR, Bates D, Black DM. Clinical use of bone Densitometry: Scientific Review. JAMA. 2002;288(15):1889-1897.

8. Gordon CM. Evaluation of bone density in children. Current opinion in Endocrinology and Diabetes. 2005;12:444-451.

9 . Genant GK, Jiang Y. Advanced imaging assessment of bone quality. Annals New York Academy of Sciences. 2006;1068: 410-428.

10. Holm IA. Challenges in clinical assessment of bone density and quality in children. Current opinion in endocrinology & Diabetes. 2006;13:15-20.

11 . Lewiecki EM, Kendler DL, Kiebzak GM et al. Special report on the official positions of the International Society for Clinical Densitometry. Osteoporosis International. 2004;156:779-784.

12. Agarwal M, Camacho P. Bone densitometry: Interpretation and pitfalls. Postgraduate Medicine. 2006;119(1):17-23.

13. Wren TAL, Liu X, Pitukcheewanont P et al. Bone acquisition in healthy children and adolescents: comparisons of dual-energy x-ray absorptiometry and computed tomography measures. The Journal of Clinical endocrinology & Metabolism. 2005;90(4):1925-1928.

14 . Pitukcheewanont P, Safani D, Church J, Gilsanz V. Bone measures in HIV-1-infected children and adolescents: disparity between quantitative computed tomography and dual energy X-ray absorptiometry measurements. Osteoporos Int. 2005;16:1393-1396.

15. Hernandez-Prado B, Lazcano-Ponce E, Cruz-Valdez A et al. Validity of bone mineral density measurements in distal sites as an indicator of total bone mineral density in a group of pre-adolescent and adolescent Women. Archives of Medical Research. 2002;33:33-39.

16 . Ikeda Y, Iki M, Morita A et al. Ultrasound bone densitometry of the calcaneous, determined with Sahara, in healthy Japanese adolescents: Japanese Population-based Osteoporosis (JPOS) Study. J Bone Miner Metab, 2004;22:248-253.

17. Azcona C, Burghard E, Ruza E et al. Reduced bone mineralization in adolescent survivors of malignant bone tumors: comparison of quantitative ultrasound and dual-energy absorptiometry. Journal of Pediatric Heamatology/Oncology. 2003;25(4):297-302.

18. Baroncelli GI, Federico G, Bertelloni S et al. Assessment of bone quality by quantitative ultrasound of proximal phalanges of the hand and fracture rate in children and adolescents with bone and mineral disorders. Pediatric Research. 2003;54:125-136.

19 . Van Rijn RR, Boot A, Wittenberg R et al. Direct X-ray radiogrammetry versus dual-energy X-ray absorptiometry: assessment of bone density in children treated for acute lymphoblastic leukaemia and growth hormone deficiency. Pediatr Radio. 2006;36:227-232

9. APPENDICES

Appendix 1- Levels of Evidence Scale

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with ≥ 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses ††††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good†††reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies

3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

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Notes

Users can add a minus-sign "-" to denote the level of that fails to provide a conclusive answer because of:

- EITHER a single result with a wide Confidence Interval (such that, for example, an ARR in an RCT is not statistically significant but whose confidence intervals fail to exclude clinically important benefit or harm)
- OR a Systematic Review with troublesome (and statistically significant) heterogeneity.
- Such evidence is inconclusive, and therefore can only generate Grade D recommendations.

*	By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be worrisome, and not all worrisome heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a "-" at the end of their designated level.
†	Clinical Decision Rule. (These are algorithms or scoring systems which lead to a prognostic estimation or a diagnostic category.)
‡	See note #2 for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
§	Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
§§	By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded), objective way in both cases and controls and/or failed to identify or appropriately control known confounders.

§ § §	Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.
† †	An "Absolute SpPin" is a diagnostic finding whose Specificity is so high that a Positive result rules-in the diagnosis. An "Absolute SnNout" is a diagnostic finding whose Sensitivity is so high that a Negative result rules-out the diagnosis.
‡ ‡	Good, better, bad and worse refer to the comparisons between treatments in terms of their clinical risks and benefits.
† † †	Good reference standards are independent of the test, and applied blindly or objectively to applied to all patients. Poor reference standards are haphazardly applied, but still independent of the test. Use of a non-independent reference standard (where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference') implies a level 4 study.
† † † †	Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive.
* *	Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using a regression analysis) to find which factors are 'significant'.
* * *	By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.
* * * *	Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (eg 1-6 months acute, 1 - 5 years chronic)

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies ***or*** extrapolations from level 1 studies
C	level 4 studies ***or*** extrapolations from level 2 or 3 studies
D	level 5 evidence ***or*** troublingly inconsistent or inconclusive studies of any level

"Extrapolations" are where data is used in a situation which has potentially clinically important differences than the original study situation.

Appendix 2 -Abbreviations

DXA	-	dual energy absorptiometry
DXR	-	direct x-ray radiogrammetry
QCT	-	quantitative computed tomography
QUS	-	quantitative ultrasound ,
pDXA	-	peripheral DXA
pQCT	-	peripheral QCT
pQUS	-	peripheral quantitative ultrasound
MRI	-	magnetic resonance imaging
BMD	-	bone mineral density
BMC	-	bone mineral content
BMI	-	body mass index
aBMD	-	areal bone mineral density
vBD	-	volumetric bone density
BTT	-	Bone transmission time
hBTT	-	humerus BTT
BUA	-	broadband ultrasound attenuation
CA	-	cortical area
LTM	-	lean tissue mass
TA	-	total area
SOS	-	speed of sound
AD-SoS	-	amplitude-dependent speed of sound